MEDICAL PROGRESS

Vitamin B_{12} deficiency in children and adolescents

Sonja A. Rasmussen, MD, MS, Paul M. Fernhoff, MD, and Kelley S. Scanlon, PhD, RD

Vitamin B_{12} (cobalamin) deficiency has been previously thought to be rare in children; however, recent studies[1] suggest that the condition is more common than previously recognized. Vitamin B_{12} deficiency in children often presents with nonspecific manifestations, such as developmental delay, irritability, weakness, and failure to thrive. Treatment may resolve these complications, but permanent neurologic damage may have already occurred. Familiarity with risk factors, manifestations, and diagnostic studies of vitamin B_{12} deficiency by pediatric health care providers is crucial to enable early recognition and treatment.

As of January 1, 1998, enriched cereal grains in the United States are mandated to contain folic acid because of its ability to prevent neural tube defects.[2] Discussions about folic acid fortification have addressed the potential for harmful effects of folic acid in adults with unrecognized vitamin B_{12} deficiency,[3-5] but vitamin B_{12} deficiency in children has not been addressed. The Institute of Medicine recently set tolerable upper intake levels of folic acid for children[6]; however, these levels were extrapolated from information on the effects of folic acid on vitamin B_{12} deficiency in adults. This article reviews the causes of vitamin B_{12} deficiency in children and adolescents, as well as its clinical manifestations, recommended laboratory studies, and treatment. In addition, we address the evidence of the potential risk for adverse effects of folic acid fortification in children and adolescents who have vitamin B_{12} deficiency.

Vitamin B_{12} and Its Metabolism

Vitamin B_{12} is found primarily in foods of animal origin. When consumed, vitamin B_{12} is released from food proteins in the stomach and binds to R-binder proteins, made in the saliva and stomach. After exposure to pancreatic proteases, vitamin B_{12} is released from the R proteins in the small intestine and forms a complex with intrinsic factor, produced in gastric parietal cells. The intrinsic factor–vitamin B_{12} complex is taken up in the terminal ileum, after recognition by specific ileal receptors. The complex dissociates in the enterocyte, and the free vitamin enters the portal circulation bound to transcobalamin II, which transports vitamin B_{12} to tissues.[7] Vitamin B_{12} is secreted in bile and reabsorbed in the ileum, conserving B_{12} in individuals with normal absorption. Although the adult recommended dietary allowance for vitamin B_{12} is 2.4 μg/d, an adult stores about 2 to 3 mg (primarily in the liver).[6] Therefore several years of dietary deficiency are usually necessary before the condition is clinically apparent.

CoA	Coenzyme A
MMA	Methylmalonic acid
NHANES III	National Health and Nutrition Examination Survey III
OMIM	Online Mendelian Inheritance in Man

Vitamin B_{12} is a cofactor for two important metabolic reactions, methylation of homocysteine to methionine and conversion of methylmalonyl coenzyme A to succinyl CoA (Figure).[8] When B_{12} is deficient, these precursors accumulate; thus, measurement of homocysteine and methylmalonic acid is useful for diagnosis of vitamin B_{12} deficiency.

Manifestations

The primary clinical manifestations of vitamin B_{12} deficiency in children and adolescents are included in Table I.[9-11] Vitamin B_{12} is necessary for production of tetrahydrofolate, important for DNA synthesis. Delayed DNA synthesis in the rapidly growing hematopoietic cells may result in macrocytic anemia,[12] seen in some cases of vitamin B_{12} deficiency. Other

From Division of Birth Defects, Child Development, and Disability and Health (proposed), National Center for Environmental Health, Atlanta, Georgia; Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; Division of Medical Genetics, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia.

Submitted for publication Mar 22, 2000; revisions received July 14, 2000, and Aug 31, 2000; accepted Oct 4, 2000.

Reprint requests: Sonja A. Rasmussen, MD, MS, 4770 Buford Hwy, NE, MS-F45, Centers for Disease Control and Prevention, Atlanta, GA 30341.

J Pediatr 2001;138:10-7.
9/19/112160
doi:10.1067/mpd.2001.112160

Table I. Clinical manifestations of vitamin B_{12} deficiency in children

General
Weakness
Fatigue
Anorexia
Failure to thrive
Irritability
Neurologic/psychiatric
Developmental delay/regression
Paresthesias
Impaired vibratory and proprioceptive sense
Hypotonia
Seizures
Ataxia
Dementia
Paralysis
Abnormal movements
Memory loss
Personality change
Poor school performance
Depression
Hematologic
Macrocytosis
Anemia
Hypersegmentation of neutrophils
Leukopenia
Thrombocytopenia
Pancytopenia
Other features
Glossitis
Skin hyperpigmentation
Vomiting/diarrhea
Icterus
Systolic flow murmur

hematologic abnormalities are also seen (Table I), and in some cases, have raised concern about a neoplastic process.[13] Neurologic changes can occur without hematologic abnormality. These include paresthesias, sensory deficits, and loss of deep tendon reflexes; movement disorders[14]; developmental regression[10]; hypotonia[10]; seizures[10]; dementia[15]; paralysis[15]; and neuropsychiatric changes (eg, depression).[16] Magnetic resonance imaging findings include increased signals on T_2-weighted images of the spinal cord,[17] brain atrophy,[18,19] and retarded myelination.[18] Neurologic deterioration has occurred in persons with unrecognized vitamin B_{12} deficiency after exposure to the anesthetic nitrous oxide.[20] Nitrous oxide inactivates the active form of vitamin B_{12} necessary for methyl transferase enzyme activity in the brain. When neurologic deterioration occurs after nitrous oxide exposure, vitamin B_{12} deficiency should be considered.

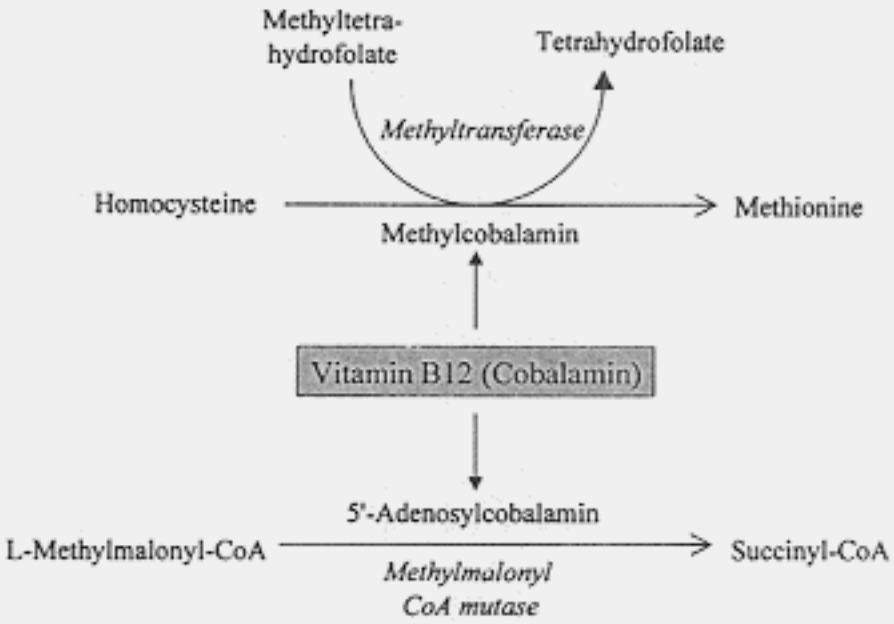

Figure. Vitamin B_{12} (cobalamin) is essential to two metabolic reactions: the methylation of homocysteine to methionine, catalyzed by N^5-methyltetrahydrofolate:homocysteine methyltransferase (referred to here as methyltransferase), which requires methylcobalamin, and the conversion of methylmalonyl CoA to succinyl CoA, catalyzed by the enzyme methylmalonyl CoA mutase, which requires 5′-adenosylcobalamin. From Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. Copyright 1995, The McGraw-Hill Companies. Adapted with permission of The McGraw-Hill Companies.

Abnormal skin pigmentation has been seen in vitamin B_{12} deficiency.[9] Failure to thrive, irritability, systolic flow murmurs, glossitis, weakness, anorexia, vomiting, constipation, diarrhea, and icterus have also been seen.[11,21]

CAUSES

Causes of vitamin B_{12} deficiency in children fall into 3 categories: decreased intake, abnormal absorption, and inborn errors of vitamin B_{12} transport and metabolism (Table II).[11,22,23]

Decreased Intake

Daily vitamin B_{12} requirements for children and adolescents range from 0.4 to 2.4 μg.[6] levels exceeded in the typical Western diet. Based on data from the third National Health and Nutrition Examination Survey (1988-1994), more than 95% of children in the United States consume more than 2.4 μg of vitamin B_{12} daily.[6] The most frequent reports of pediatric vitamin B_{12} deficiency related to decreased intake have occurred in breast-fed infants of mothers who have undiagnosed vitamin B_{12} deficiency because of strict vegetarian diets,[10,19,24] unrecognized pernicious anemia,[10,24] previous gastric bypass surgery,[25] or short gut syndrome.[10] Vitamin B_{12} levels in breast milk parallel those in the serum.[26] Normally, a newborn has 25 μg of total B_{12} content in the liver, an amount predicted to be sufficient until the end of the first year of life, even with low intake.[7] However, fetal B_{12} storage is significantly decreased in mothers with vitamin B_{12} deficiency[27];

Table II. Causes of vitamin B_{12} deficiency in children

Decreased intake
Strict vegetarian/vegan/macrobiotic diet
Breast-fed infants of mothers with unrecognized vitamin B_{12} deficiency secondary to pernicious anemia, vegetarian diet, gastric bypass
Atypical diets (ie, poor diet, poorly controlled PKU)
Abnormal absorption
Absence/dysfunction of intrinsic factor
Status after gastric resection
Autoimmune pernicious anemia
Absent/abnormal formation of intrinsic factor (autosomal recessive)
Decreased gastric acid
Long-term therapy with medications that decrease gastric acid secretion
Pancreatic insufficiency
Competition for B_{12} in intestine
Parasitic infection
Bacterial overgrowth
Disruption of absorption across ileal surface
Crohn's disease
Celiac disease
Surgical procedures involving ileum
Abnormal ileal receptor (Imerslund-Gräsbeck disease)
Inborn errors of B_{12} transport and metabolism
Abnormal transport
Transcobalamin II deficiency
R-binder deficiency
Abnormal metabolism
Adenosylcobalamin deficiency: *cbl*A and *cbl*B diseases
Methylcobalamin deficiency: *cbl*E and *cbl*G diseases
Combined adenosylcobalamin and methylcobalamin deficiencies: *cbl*C, *cbl*D, and *cbl*F

PKU, Phenylketonuria.

because of these decreased stores, breast-fed infants with low postnatal B_{12} intake associated with maternal deficiency may present as early as 3 to 4 months of age. Because manifestations at this age are often nonspecific, pediatric health care providers need to be vigilant for conditions (eg, pernicious anemia) that can produce vitamin B_{12} deficiency in mothers with normal B_{12} intake and adversely affect their breast-fed infants.

Children and adolescents on atypical diets may also develop vitamin B_{12} deficiency. Severe neurologic manifestations were seen in an adolescent with vitamin B_{12} deficiency associated with a strict vegetarian diet.[28] Adults who were long-term strict vegans had significantly lower B_{12} levels than a population on an unrestricted diet[29] and often had evidence of vitamin B_{12} deficiency.[30] However, megaloblastic anemia was infrequently observed, which was attributed to their high folic acid intake.[29] Low B_{12} intake and levels, as well as elevated blood and urine MMA levels, have also been observed in a significant proportion of children on macrobiotic diets.[31,32] Other non-vegetarian diets associated with vitamin B_{12} deficiency in children and adolescents include nutritionally inadequate diets, because foods low in vitamin B_{12} are often selected.[21] In addition, adolescents and young adults with phenylketonuria who exclude animal products in an effort to decrease phenylalanine levels but are not compliant with their medical formula may develop vitamin B_{12} deficiency.[33] Deficiency of vitamin B_{12} and other nutrients has also been observed in an adolescent with glycogen storage disease type Ib, also on a restricted diet.[34]

Abnormal Absorption

Abnormal vitamin B_{12} absorption may occur as the result of an absent or abnormal intrinsic factor, decreased B_{12} release from food protein, failure of R-protein degradation, competition for B_{12} absorption at the ileum, loss of the ileal absorptive surface, or an abnormal ileal receptor.[23]

Vitamin B_{12} deficiency, caused by absent intrinsic factor, has been reported in children after gastric resection.[35] The classic adult form of autoimmune pernicious anemia is rare in children.[11] Some children with autoimmune pernicious anemia have other autoimmune conditions as part of autoimmune polyglandular syndrome type I (Online Mendelian Inheritance in Man 240300).[36] An autosomal recessive condition in which intrinsic factor is absent or abnormal has also been reported (OMIM 261000).[36]

Vitamin B_{12} release from dietary proteins requires gastric acid; thus, children receiving medications that affect gastric acid secretion (eg, omeprazole) on a long-term basis may be at risk for B_{12} malabsorption.[37] Pancreatic proteases are responsible for R-protein degradation from vitamin B_{12}, but pancreatic insufficiency appears to be a rare cause of B_{12} deficiency in children.[38] Competition for B_{12} in the intestinal lumen may cause vitamin B_{12} malabsorption. Low B_{12} levels have been seen in cases of infection with *Giardia lamblia*, *Plasmodium falciparum*, *Diphyllobothrium latum* (tapeworm), and *Strongyloides stercoralis* (roundworm).[39]

Disruption of the ileal surface can affect B_{12} absorption; thus, patients with tropical sprue, Crohn's disease, and celi-

ac disease[40] are at risk for vitamin B_{12} deficiency. Vitamin B_{12} deficiency has also been observed in children who have undergone limited ileal resection.[41]

Imerslund-Gräsbeck syndrome (OMIM 261100),[36] an autosomal recessive condition in which B_{12} malabsorption is due to an abnormal ileal receptor, is diagnosed on the basis of selective B_{12} malabsorption that is not corrected by administration of intrinsic factor. The responsible gene, cubilin (OMIM 602997),[36] has been identified, and its product serves as the ileal receptor for the intrinsic factor–vitamin B_{12} complex.

Adults with human immunodeficiency virus infection may have low vitamin B_{12} levels, possibly related to malabsorption, although deficiency appears to be infrequent.[42] The frequency of vitamin B_{12} deficiency in children with human immunodeficiency virus infection is unknown.

Inborn Errors of Vitamin B_{12} Transport and Metabolism

Although inborn errors of cobalamin transport and cellular utilization share some features with the forms of B_{12} deficiency previously discussed, manifestations, diagnostic methods, and treatment differ. A full discussion of these conditions is not possible in this review; therefore, in Table III we have summarized information from the excellent reviews of these conditions.[8,22,36]

The defects of cellular cobalamin utilization can be divided into abnormalities in synthesis of adenosylcobalamin (designated *cbl*A and *cbl*B), of methylcobalamin (*cbl*E and *cbl*G), and of both cofactors (*cbl*C, *cbl*D, and *cbl*F). Methylmalonic aciduria caused by deficiency of methylmalonyl CoA mutase (the enzyme for which adenosylcobalamin serves as a cofactor) (OMIM 251000)[36] is not included here, because patients do not respond well to vitamin B_{12} therapy. All these conditions are believed to be autosomal recessive, except the autosomal dominant R-binder deficiency.

DIAGNOSIS

Previously, macrocytic anemia had been assumed to be nearly always present in vitamin B_{12} deficiency; however, further examination argues against this assumption. Fine and Soria[43] estimate that reliance on an abnormal hemoglobin value, hematocrit, or mean corpuscular volume for a diagnosis of B_{12} deficiency would miss about 30% of adult cases. Macrocytosis can be masked by other conditions (eg, iron deficiency anemia and thalassemia).[43] Although the peripheral blood smear is often abnormal (with oval macrocytes and hyper-segmented neutrophils), this finding is not sensitive or specific for mild cases.[12] Thus the diagnosis should not depend on the finding of abnormal hematologic values. Further, macrocytosis is not specific for B_{12} deficiency in children, because several other causes have been noted.[44]

Measurement of vitamin B_{12} levels can be helpful for diagnosing vitamin B_{12} deficiency. Serum or plasma B_{12} levels vary, depending on the laboratory and the method used[6]; therefore, laboratories should determine their own range of results.[45] Generally, normal serum B_{12} levels range from 200 to 900 pg/mL, and levels below 80 are almost always indicative of vitamin B_{12} deficiency.[45] However, the B_{12} level is normal in patients with some inborn errors of vitamin B_{12} metabolism (Table III), because vitamin B_{12} is present but unavailable to tissues as a result of abnormal transport or utilization. In addition, because tissue levels may become depleted before serum levels, some persons with borderline or low-normal serum vitamin B_{12} levels have had symptoms that resolved with B_{12} treatment, suggesting that levels previously considered borderline or normal may represent deficiency in some patients.[46]

Holo-transcobalamin II (cobalamin bound to transcobalamin II) levels may be an early indicator of vitamin B_{12} deficiency, because vitamin B_{12} is preferentially depleted from holo-transcobalamin II.[47] However, holo-transcobalamin II levels were not specific for vitamin B_{12} deficiency in a study of macrocytosis,[48] which diminishes their usefulness. The deoxyuridine suppression test examines a metabolic pathway of DNA synthesis that indirectly requires methylcobalamin and is a sensitive method for identifying vitamin B_{12} deficiency. However, this test is performed only in specialized laboratories and optimally requires a bone marrow aspirate.[47]

Two precursors in the metabolic pathways affected by vitamin B_{12} (Figure), MMA and homocysteine, are elevated in vitamin B_{12} deficiency, including inborn errors of vitamin B_{12} utilization. Homocysteine metabolism is also affected by levels of folic acid and vitamin B_6, whereas increased MMA levels are specific for deficiency of vitamin B_{12} (or abnormalities in the methylmalonyl CoA mutase enzyme). Therefore evaluation of both MMA and total homocysteine is helpful in distinguishing between folate deficiency and vitamin B_{12} deficiency. Measurement of serum MMA appears to be highly sensitive for the diagnosis of vitamin B_{12} deficiency.[49] MMA levels had the highest discriminative power to distinguish 41 infants receiving a macrobiotic diet from 50 healthy omnivorous control subjects.[33]

Studies are needed to determine the optimum strategy for diagnosis of vitamin B_{12} deficiency in children. We recommend studying vitamin B_{12}, MMA, and total homocysteine levels in any child with features of unknown etiology consistent with vitamin B_{12} deficiency (Table I). After vitamin B_{12} deficiency is diagnosed, further studies are often necessary to determine the cause. These may include a full dietary evaluation; evaluation for parasitic infections; Schilling test (crystalline radioactive B_{12} is provided orally and urinary B_{12} excretion is measured), which measures the patient's ability to absorb oral crystalline vitamin B_{12}[47]; modified Schilling test (food-bound radioactive B_{12} is provided orally, followed by measurement of urinary B_{12}), which mea-

Table III. Inborn errors of cobalamin transport and metabolism[8,22,36]

Condition (OMIM No.)	Defect	Typical clinical manifestations	Typical onset
TCII deficiency (OMIM 275350)	Defective/absent TCII	Failure to thrive, megaloblastic anemia, later neurologic features, and immunodeficiency	Early infancy
R-binder deficiency (OMIM 193090)	Deficiency/absence of TCI in plasma, saliva, leukocytes	Neurologic symptoms reported, but unclear if these are related to condition	Unclear if observed symptoms are related to condition
Defective synthesis of AdoCbl: *cbl*A (OMIM 251100) *cbl*B (OMIM 251110)	Defective synthesis of AdoCbl	Lethargy, failure to thrive, recurrent vomiting, dehydration, hypotonia	Infancy
Defective synthesis of MeCbl: *cbl*E (OMIM 236270) *cbl*G (OMIM 250940)	Defective synthesis of MeCbl	Vomiting, poor feeding, lethargy, severe neurologic dysfunction, megaloblastic anemia	Most in infancy, at least one adult
Defective synthesis of AdoCbl and MeCbl: *cbl*C (OMIM 277400) *cbl*D (OMIM 277410) *cbl*F (OMIM 277380)	Impaired synthesis of both AdoCbl and MeCbl	Failure to thrive, developmental delay, neurologic dysfunction, megaloblastic anemia, some cases with retinal findings, hemolytic uremic syndrome	Variable from neonatal period to adolescence, majority with neonatal onset

TCII, Transcobalamin II; *OMIM,* Online Mendelian Inheritance in Man; *Cbl,* cobalamin; *MMA,* methylmalonic acid; *TCI,* transcobalamin I; *AdoCbl,* adenosylcobalamin; *MeCbl,* methylcobalamin.

sures absorption of protein-bound vitamin[47]; amino acid analysis; measurement of the unsaturated B_{12}-binding capacity and transcobalamin II levels[50]; genetic complementation studies on cultured fibroblasts; and measurement of antibodies to parietal cells and intrinsic factor. Subspecialty consultation is often necessary to guide these studies.

PREVALENCE

Information about the prevalence of vitamin B_{12} deficiency in the United States is limited; however, a study of serum B_{12} levels in 3766 children (aged 4 to 19 years), as part of the second phase of NHANES III (1991-1994), identified 3 children with levels <100 pg/mL, a frequency of 1 in 1255, and 18 with levels <200 pg/mL, a frequency of 1 in 200.[1] The greatest proportion of children with levels <200 pg/mL was found in the 12- to 19-year age category, with a rate of 1 in 112. The lowest mean levels were in the 12- to 19-year category and in non-Hispanic whites. No further information about the cause of these low B_{12} levels, presence of symptoms, or follow-up studies has been reported. However, these data suggest that B_{12} deficiency may be more common than previously recognized.[22]

Data from two newborn screening programs, which included a screen for elevated urinary MMA levels in infants aged 3 to 4 weeks, indicate a frequency of "symptomatic" methylmalonic aciduria of 1 in 77,000 to 1 in 83,000 births.[51,52] More than half the cases with definitive diagnoses had defects in cobalamin synthesis, and the remainder had deficiency of methylmalonyl CoA mutase. In one program, 40 infants with "relatively small amounts" of MMA were identified,[51] a frequency of 1 in 7300. These asymptomatic infants were primarily breast fed,[51] and some may have had subclinical vitamin B_{12} deficiency. However, the sensitivity of this method to detect mild deficiency is unknown.

A much higher frequency of B_{12} deficiency than that seen in the United States has been observed in countries with lower intake of animal products.[53,54] For example, 22% of school-aged children from rural communities in Mexico had a deficient plasma B_{12} level,

Laboratory findings	Treatment and response	Gene identified?
Usually normal serum Cbl; elevated serum MMA, homocysteine; absent/defective TCII	High doses of Cbl by injection; good response to treatment if begun early	Yes: TCN2 (OMIM 275350)
Low serum Cbl, normal TCII-Cbl levels	Cbl therapy does not appear to be of benefit	No
Normal serum Cbl, homocysteine, and methionine; elevated MMA, ketones, glycine, ammonia; leukopenia, thrombocytopenia, anemia	Pharmacologic doses of Cbl, dietary protein restriction, oral antibiotics; treatment response for *cbl*A better than for *cbl*B	No
Normal serum Cbl and folate; homocystinuria, hypomethioninemia	Pharmacologic doses of Cbl, betaine; good treatment response in some patients treated early	Yes: methionine synthase reductase (OMIM 602568) for *cbl*E and methionine synthase (OMIM 156570) for *cbl*G
Normal serum Cbl, TCII; methylmalonic aciduria, homocystinuria, hypomethioninemia	Pharmacologic doses of hydroxocobalamin, moderate protein restriction, betaine; treatment response often not optimal	No

defined as <103 pmol/L (about 140 pg/mL).[54] Inadequate B_{12} intake was responsible for a portion of this deficiency, but B_{12} malabsorption (thought to be secondary to *Giardia lamblia* infection and bacterial overgrowth) was seen in about one fourth of this population.[54]

Potential Effects of Folic Acid Fortification on Vitamin B_{12}–Deficient Children

In adults, it has been suggested that the neurologic effects of vitamin B_{12} deficiency may be precipitated or aggravated by folic acid administration, possibly because of a direct effect of folic acid. However, the clinical evidence for this has been questioned by some authors.[3,4,55] In children, evidence for a direct effect of folic acid is particularly scant. We identified 6 children with vitamin B_{12} deficiency[56-62] (receiving folic acid because of an incorrect diagnosis) in whom it has been suggested that folic acid therapy worsened the neurologic manifestations. However, in all cases, diagnosis and appropriate treatment with B_{12} had been substantially delayed, and the deterioration observed was similar to that seen with delay in treatment. Therefore it is unclear whether the folic acid therapy or delay in B_{12} treatment was responsible for the neurologic manifestations.[22] In addition, in the 3 children for whom adequate dosage information was available,[57,58,60] doses ranged from 5 mg to 15 mg of synthetic folic acid per day for long periods. A recent study of dietary folate intake in the US population suggests that these doses are unlikely to be reached through diet, even after adjustment for current fortification levels.[63] This study used dietary folate equivalents as a measure of folate intake, which adjust for the apparent greater bioavailability of synthetic folic acid compared with naturally occurring folate. The 99th percentile for dietary folate equivalents in the age group with the highest level of folate intake (aged 1-5 years) was about 1.5 mg/d (equivalent to about 0.9 mg/d synthetic folic acid). Based on these data, it appears unlikely that children would exceed 5 mg of folic acid intake per day at the current level of fortification and intake, or even if food fortification levels were increased from 1.4 mg/kg to 3.5 mg/kg grain, as has been proposed.[64] However, the effects of daily folic acid intake of <5 mg in children who have vitamin B_{12} deficiency have not been systematically studied.

Because of the paucity of data in children, the Institute of Medicine[6] established tolerable upper limits (the highest level likely to pose no adverse health effects to almost all individuals in the general population) of folic acid intake, based on the adult level of 1000 µg/d, adjusted for relative body weight. The upper limits set for children ranged from 300 µg/d for children aged 1 to 3 years to 800 µg/d for those aged 14 to 18 years.[6] It should be noted that many children currently consume higher levels,[63] as was the case for some children before fortification. Additional data are needed to determine whether there is any evidence of increased risk for adverse effects in children.

Another concern is that folic acid may mask the hematologic changes of vitamin B_{12} deficiency, leading to a delay in diagnosis and worsening of neurologic manifestations. Folic acid may reverse the hematologic abnormal-

ities that sometimes occur with vitamin B_{12} deficiency.[55] The frequency of masking hematologic abnormalities by the folic acid levels achieved by fortification is unknown, but hematologic abnormalities are not reliably found in vitamin B_{12} deficiency. Health care providers need to realize that hematologic indices are normal in a substantial proportion of children with vitamin B_{12} deficiency and that this proportion may increase because of fortification of the food supply with folic acid.

TREATMENT

Treatment of vitamin B_{12} deficiency depends on its cause. In mild, asymptomatic deficiency, altering the diet or correcting an underlying condition may be appropriate, but in most cases, administration of vitamin B_{12} is necessary. Dosage has not been well established in children. Because hypokalemia has been observed during treatment initiation in adults with severe anemia,[65] low initial cyanocobalamin doses (0.2 μg/kg, given subcutaneously for 2 days), as well as potassium supplements as needed and transfusion for partial correction of the anemia, have been recommended for children with severe anemia.[11] These low initial doses are followed by 1000 μg/day, given subcutaneously, for 2 to 7 days, and subsequent weekly doses of 100 μg for a month.[11] For malabsorptive causes of vitamin B_{12} deficiency, long-term treatment is often necessary; monthly maintenance doses of 100 μg have been recommended.[11] Size and frequency of doses need to be carefully titrated in relation to clinical response and laboratory values. Children with defects in vitamin B_{12} transport and metabolism often require massive doses of cobalamin and additional forms of treatment (Table III).

Although treatment results in a dramatic clinical and laboratory response in most patients, neurologic damage may persist. Long-term prognosis appears related to the severity and duration of deficiency,[19] emphasizing the importance of early diagnosis and treatment.

Recently, interest in oral therapy for vitamin B_{12} deficiency in adults has arisen.[66] A randomized controlled trial demonstrated that oral and parenteral therapy were equally effective in the treatment of adults with B_{12} deficiency[66]; however, no data are available about use of oral vitamin B_{12} replacement in children.

We thank Drs Barbara Bowman and J. David Erickson for their helpful comments.

REFERENCES

1. Wright JD, Bialostosky K, Gunter EW, Carroll MD, Najjar MF, Bowman BA, et al. Blood folate and vitamin B12: United States, 1988-94. Vital Health Stat 1998;11:1-78.
2. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327:1832-5.
3. Bower C, Wald NJ. Vitamin B12 deficiency and the fortification of food with folic acid. Eur J Clin Nutr 1995; 49:787-93.
4. Dickinson CJ. Does folic acid harm people with vitamin B12 deficiency? QJM 1995;88:357-64.
5. Tucker KL, Mahnken B, Wilson PW, Jacques P, Selhub J. Folic acid fortification of the food supply. Potential benefits and risks for the elderly population. JAMA 1996;276:1879-85.
6. Food and Nutrition Board Institute of Medicine. Vitamin B12 dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington (DC): National Academy Press; 1998. p. 8-1-9-33.
7. Allen LH. Vitamin B12 metabolism and status during pregnancy, lactation and infancy. Adv Exp Med Biol 1994; 352:173-86.
8. Fenton W, Rosenberg LE. Inherited disorders of cobalamin transport and metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill, Inc; 1995. p. 3129-49.
9. Sabatino D, Kosuri S, Remollino A, Shotter B. Cobalamin deficiency presenting with cutaneous hyperpigmentation: a report of two siblings. Pediatr Hematol Oncol 1998;15:447-50.
10. Monagle PT, Tauro GP. Infantile megaloblastosis secondary to maternal vitamin B12 deficiency. Clin Lab Haematol 1997;19:23-5.
11. Whitehead VM, Rosenblatt RD, Cooper BA. Megaloblastic anemia. In: Nathan DG, Orkin SH, editors. Nathan and Oski's hematology of infancy and childhood. Philadelphia: WB Saunders Company; 1998. p. 385-422.
12. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Intern Med 1999;159:1289-98.
13. Chintagumpala MM, Dreyer ZA, Steuber CP, Cooley LD. Pancytopenia with chromosomal fragility: vitamin B12 deficiency. J Pediatr Hematol Oncol 1996;18:166-70.
14. Emery ES, Homans AC, Colletti RB. Vitamin B12 deficiency: a cause of abnormal movements in infants. Pediatrics 1997;99:255-6.
15. Al Essa M, Sakati NA, Dabbagh O, Joshi S, Al Jishi EA, Rashed MS, et al. Inborn error of vitamin B12 metabolism: a treatable cause of childhood dementia/paralysis. J Child Neurol 1998;13:239-43.
16. Middleman AB, Melchiono MW. A routine CBC leads to a nonroutine diagnosis. Adolesc Med 1996;7:423-6.
17. Wolansky LJ, Goldstein G, Gozo A, Lee HJ, Sills I, Chatkupt S. Subacute combined degeneration of the spinal cord: MRI detection of preferential involvement of the posterior columns in a child. Pediatr Radiol 1995;25:140-1.
18. Løvblad K, Ramelli G, Remonda L, Nirkko AC, Ozdoba C, Schroth G. Retardation of myelination due to dietary vitamin B12 deficiency: cranial MRI findings. Pediatr Radiol 1997;27:155-8.
19. von Schenck U, Bender-Gotze C, Koletzko B. Persistence of neurological damage induced by dietary vitamin B-12 deficiency in infancy. Arch Dis Child 1997;77:137-9.
20. Lee P, Smith I, Piesowicz A, Brenton D. Spastic paraparesis after anaesthesia. Lancet 1999;353:554.
21. Middleman AB, Emans SJ, Cox J. Nutritional vitamin B12 deficiency and folate deficiency in an adolescent patient presenting with anemia, weight loss, and poor school performance. J Adolesc Health 1996;19:76-9.
22. Rosenblatt DS, Whitehead VM. Cobalamin and folate deficiency: acquired and hereditary disorders in children. Semin Hematol 1999;36:19-34.
23. Schjonsby H. Vitamin B12 absorption and malabsorption. Gut 1989;30:1686-91.

24. Graham SM, Arvela OM, Wise GA. Long-term neurologic consequences of nutritional vitamin B12 deficiency in infants. J Pediatr 1992;121:710-4.
25. Grange DK, Finlay JL. Nutritional vitamin B12 deficiency in a breastfed infant following maternal gastric bypass. Pediatr Hematol Oncol 1994;11:311-8.
26. Specker BL, Black A, Allen L, Morrow F. Vitamin B-12: low milk concentrations are related to low serum concentrations in vegetarian women and to methylmalonic aciduria in their infants. Am J Clin Nutr 1990;52:1073-6.
27. Baker SJ, Jacob E, Rajan KT, Swaminathan SP. Vitamin-B12 deficiency in pregnancy and the puerperium. Br Med J 1962;1:1658-61.
28. Ashkenazi S, Weitz R, Varsano I, Mimouni M. Vitamin B12 deficiency due to a strictly vegetarian diet in adolescence. Clin Pediatr (Phila) 1987;26:662-3.
29. Bar-Sella P, Rakover Y, Ratner D. Vitamin B12 and folate levels in long-term vegans. Isr J Med Sci 1990;26:309-12.
30. Haddad EH, Berk LS, Kettering JD, Hubbard RW, Peters WR. Dietary intake and biochemical, hematologic, and immune status of vegans compared with nonvegetarians. Am J Clin Nutr 1999;70:586S-93S.
31. Dagnelie PC, van Staveren WA. Macrobiotic nutrition and child health: results of a population-based, mixed-longitudinal cohort study in The Netherlands. Am J Clin Nutr 1994;59:1187S-96S.
32. Schneede J, Dagnelie PC, van Staveren WA, Vollset SE, Refsum H, Ueland PM. Methylmalonic acid and homocysteine in plasma as indicators of functional cobalamin deficiency in infants on macrobiotic diets. Pediatr Res 1994;36:194-201.
33. Robinson M, White FJ, Cleary MA, Wraith E, Lam WK, Walter JH. Increased risk of vitamin B12 deficiency in patients with phenylketonuria on an unrestricted or relaxed diet. J Pediatr 2000;136:545-7.
34. Kishnani PS, Boney A, Chen YT. Nutritional deficiencies in a patient with glycogen storage disease type 1b. J Inherit Metab Dis 1999;22:795-801.
35. Quak SH, Joseph VT, Wong HB. Neonatal total gastrectomy. Clin Pediatr (Phila) 1984;23:507-8.
36. Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2000. http://www.ncbi.nlm.nih.gov/omim/
37. Bradford GS, Taylor CT. Omeprazole and vitamin B12 deficiency. Ann Pharmacother 1999;33:641-3.
38. Gueant JL, Champigneulle B, Gaucher P, Nicolas JP. Malabsorption of vitamin B12 in pancreatic insufficiency of the adult and of the child. Pancreas 1990;5:559-67.
39. Brasitus TA. Parasites and malabsorption. Clin Gastroenterol 1983;12:495-510.
40. Hjelt K, Krasilnikoff PA. The impact of gluten on haematological status, dietary intakes of haemopoietic nutrients and vitamin B12 and folic acid absorption in children with coeliac disease. Acta Paediatr Scand 1990;79:911-9.
41. Davies BW, Abel G, Puntis JW, Arthur RJ, Truscott JG, Oldroyd B, et al. Limited ileal resection in infancy: the long-term consequences. J Pediatr Surg 1999;34:583-7.
42. Remacha AF, Cadafalch J. Cobalamin deficiency in patients infected with the human immunodeficiency virus. Semin Hematol 1999;36:75-87.
43. Fine EJ, Soria ED. Myths about vitamin B12 deficiency. South Med J 1991;84:1475-81.
44. Pappo AS, Fields BW, Buchanan GR. Etiology of red blood cell macrocytosis during childhood: impact of new diseases and therapies. Pediatrics 1992;89:1063-7.
45. Gibson R. Principles of nutritional assessment. New York: Oxford University Press; 1990. p. 460-86.
46. Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988;318:1720-8.
47. Zittoun J, Zittoun R. Modern clinical testing strategies in cobalamin and folate deficiency. Semin Hematol 1999;36:35-46.
48. Wickramasinghe SN, Ratnayaka ID. Limited value of serum holo-transcobalamin II measurements in the differential diagnosis of macrocytosis. J Clin Pathol 1996;49:755-8.
49. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. Am J Med 1994;96:239-46.
50. Bibi H, Gelman-Kohan Z, Baumgartner ER, Rosenblatt DS. Transcobalamin II deficiency with methylmalonic aciduria in three sisters. J Inherit Metab Dis 1999;22:765-72.
51. Coulombe JT, Shih VE, Levy HL. Massachusetts Metabolic Disorders Screening Program. II. Methylmalonic aciduria. Pediatrics 1981;67:26-31.
52. Sniderman LC, Lambert M, Giguere R, Auray-Blais C, Lemieux B, Laframboise R, et al. Outcome of individuals with low-moderate methylmalonic aciduria detected through a neonatal screening program. J Pediatr 1999;134:675-80.
53. Casterline JE, Allen LH, Ruel MT. Vitamin B-12 deficiency is very prevalent in lactating Guatemalan women and their infants at three months postpartum. J Nutr 1997;127:1966-72.
54. Allen LH, Rosado JL, Casterline JE, Martinez H, Lopez P, Munoz E, et al. Vitamin B-12 deficiency and malabsorption are highly prevalent in rural Mexican communities. Am J Clin Nutr 1995;62:1013-9.
55. Campbell NR. How safe are folic acid supplements? Arch Intern Med 1996;156:1638-44.
56. Thomas PK, Hoffbrand AV, Smith IS. Neurological involvement in hereditary transcobalamin II deficiency. J Neurol Neurosurg Psychiatry 1982;45:74-7.
57. Mane JV, Vives-Corrons JL, Rozman C. Congenital folate-dependent megaloblastic anaemia of unknown aetiology. Lancet 1977;1:262-3.
58. Burman JF, Mollin DL, Sourial NA, Sladden RA. Inherited lack of transcobalamin II in serum and megaloblastic anaemia: a further patient. Br J Haematol 1979;43:27-38.
59. Conway SP, Gillies DR, Littlewood JM. Vitamin B12 neuropathy in a 6 year old. Arch Dis Child 1984;59:575-6.
60. Reisner EH, Wolff JA, McKay RJ Jr, Doyle EF. Juvenile pernicious anemia. Pediatrics 1951;8:88-106.
61. Pearson HA, Vinson R, Smith RT. Pernicious anemia with neurologic involvement in childhood. J Pediatr 1964;65:334-9.
62. Hall CA. The neurologic aspects of transcobalamin II deficiency. Br J Haematol 1992;80:117-20.
63. Lewis CJ, Crane NT, Wilson DB, Yetley EA. Estimated folate intakes: data updated to reflect food fortification, increased bioavailability, and dietary supplement use. Am J Clin Nutr 1999;70:198-207.
64. Oakley GP Jr, Adams MJ, Dickinson CM. More folic acid for everyone, now. J Nutr 1996;126:751S-5S.
65. Lawson DH, Murray RM, Parker JL, Hay G. Hypokalaemia in megaloblastic anaemias. Lancet 1970;2:588-90.
66. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. Blood 1998;92:1191-8.